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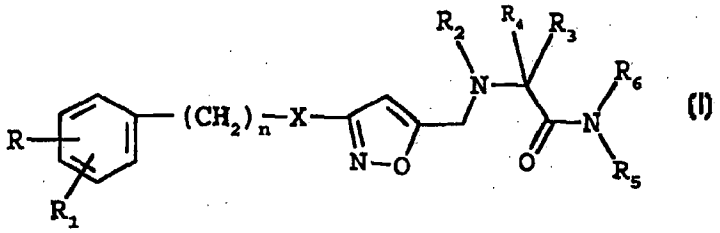

(I)

(57) **Abstract**

Novel 2-[(3-substituted)-5-isoxazolylmethylamino]alkanamides, having formula (I), wherein: n is zero or an integer of 1 to 3; X is O, S or NH; each of R and R_1, which are the same or different, is hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_4 alkoxy or trifluoromethyl; each of R_2, R_5 and R_6, which are the same or different, is hydrogen or C_1-C_6 alkyl; each of R_3 and R_4, which are the same or different, is hydrogen or C_1-C_6 alkyl or R_3 and R_4 taken together with the adjacent carbon atom form a C_3-C_7 cycloalkyl ring; and their pharmaceutically acceptable salts are active CNS agents.

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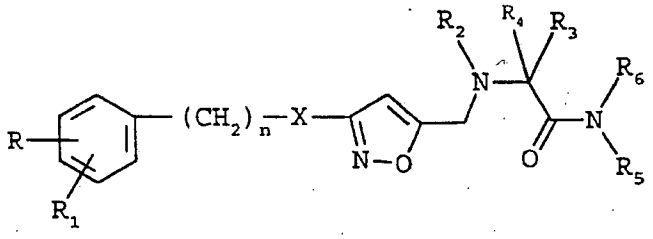
2-[(3-SUBSTITUTED)-5-ISOXAZOLYLMETHYLAMINO]ALKANAMIDE DERIVATIVES

The present invention relates to novel 2-[(3-substituted)-5-isoxazolylmethylamino]alkanamides, to their use as therapeutic agents, to a process for their preparation and to pharmaceutical compositions containing them.

It has been found that novel 2-[(3-substituted)-5-isoxazolylmethylamino]alkanamide derivatives as herein defined have valuable biological properties, in particular as antiepileptic, anti-Parkinson, neuroprotective, anti-depressant, antispastic and/or hypnotic agent.

The present invention provides compounds having the following formula (I)



(I)

wherein:

n is zero or an integer of 1 to 3;

X is O, S or NH;

each of R and R_1 independently is hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_4 alkoxy or trifluoromethyl;

each of R_2, R_5 and R_6 independently is hydrogen or C_1-C_6 alkyl;

each of R_3 and R_4 independently is hydrogen, C_1-C_6 alkyl or R_3 and R_4 taken together with the adjacent carbon atom form a C_3-C_7 cycloalkyl ring;

and their pharmaceutically acceptable salts.

The pharmaceutically acceptable salts of the compounds of

formula (I) include acid addition salts with inorganic, e.g. hydrochloric, hydrobromic, sulphuric, and phosphoric acids, or organic, e.g. acetic, propionic, lactic, oxalic, malic, maleic, tartaric, citric, benzoic, mandelic, salicylic, alkylsulfonic and fumaric acids.

The compounds of the formula (I), their pharmaceutically acceptable salts may also form pharmaceutically acceptable solvates, such as mono-, di- or tri-hydrates, which are also object of the present invention.

The alkyl and alkoxy groups may be branched or straight groups.

A C_1-C_6 alkyl group is preferably a C_1-C_4 alkyl group, in particular methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl, more preferably methyl or ethyl.

Representative examples of C_1-C_4 alkoxy groups include methoxy or ethoxy.

A halogen atom is e.g. chlorine, fluorine, bromine, in particular chlorine and fluorine, more preferably fluorine.

A C_3-C_7 cycloalkyl group is, for instance, a cyclopropyl, cyclohexyl or cycloheptyl group, in particular cyclopropyl.

Compounds of formula (I) contain an asymmetric carbon atom and have optical l and d isomers. These compounds can be used as the dl racemate or the d- and l-isomer can be separately synthesized from optically pure starting material or separated from the racemate in a conventional manner.

The present invention also include within its scope both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

Preferred compounds of the invention are the compounds of

formula (I) wherein

n is 1 or 2;

R is hydrogen;

R_1 is hydrogen or halogen;

each of R_2, R_3, R_4, R_5 and R_6 independently is hydrogen or C_1-C_4 alkyl; and the pharmaceutically acceptable salts thereof.

More preferred compounds of the invention are the compounds of formula (I), wherein

n is 1;

X is O or NH;

R_1 is hydrogen or halogen;

R_3 is C_1-C_4 alkyl;

R_4 is hydrogen or C_1-C_4 alkyl;

R, R_2, R_5 and R_6 are hydrogen;

and the pharmaceutically acceptable salts thereof.

Examples of specific compounds of the invention are:

2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide;

2-[3-(3-chlorobenzyloxy)isoxazol-5-ylmethylamino] propanamide;

2-[3-(3-bromobenzyloxy)isoxazol-5-ylmethylamino]propanamide;

2-[3-(4-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide;

2-[3-(2-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide;

2-[3-(3-fluorobenzylamino)isoxazol-5-ylmethylamino] propanamide;

2-[3-(benzylsulfanyl)isoxazol-5-ylmethylamino]propanamide;

2-{[3-(3-fluorobenzyloxy)isoxazol-5-ylmethyl]methylamino} propanamide;

2-{[3-(3-chlorobenzyloxy)isoxazol-5-ylmethyl]methylamino} propanamide;

2-{[3-(3-bromobenzyloxy)isoxazol-5-ylmethyl]methylamino} propanamide;

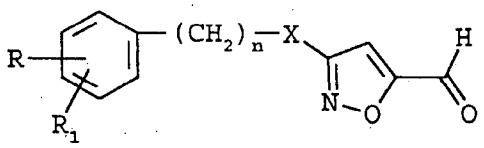
2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino]-N-methyl-propanamide;

2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino]-2-methyl-propanamide;

if the case either as a single S- or R-isomer or as a mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

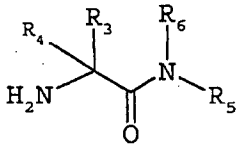
The compounds of the invention and the salts thereof can be obtained by a process comprising:

a) reaction of a compound of formula (II)



(II)

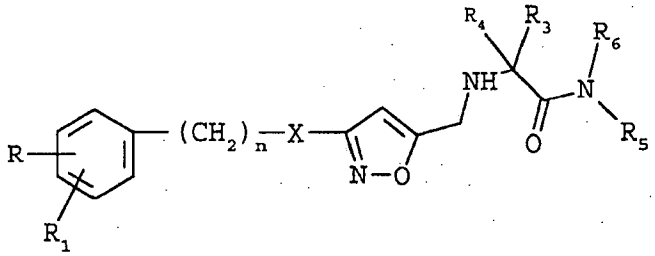
wherein n, R, R_1 and X are as defined above, with a compound of formula (III)



(III)

wherein R_3, R_4, R_5 and R_6 are as defined above, thus obtaining a compound of formula (I) in which R_2 is hydrogen; or

b) reaction of a compound of formula (IV)



(IV)

wherein R, R_1, R_3, R_4, R_5, R_6 n and X are as defined above, with a compound of formula (V) or (VI)

R'_2W (V) R''_2CHO (VI)

wherein W is a halogen atom, R'_2 is a C_1-C_6 alkyl and R''_2 is hydrogen or C_1-C_5 alkyl, thus obtaining a compound of the invention in which R_2 is C_1-C_6 alkyl; and, if desired, converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of isomers of a compound of the invention into the single isomer.

All the processes described hereabove are analogy processes and can be carried out according to well known methods in organic chemistry.

The reaction of a compound of formula (II) with a compound of formula (III) to give a compound of formula (I) or (IV) is a reductive amination reaction which can be carried out according to well known methods. According to a preferred embodiment of the invention it may be performed under nitrogen atmosphere, in a suitable organic solvent, such as an alcohol, e.g. a C_1-C_4 alkanol, in particular methanol, or in acetonitrile, at a temperature ranging from about 0°C to about 40°C, in the presence of a reducing agent, the most appropriate being sodium cyanoborohydride. Occasionally molecular sieves can be added to the reaction mixture for

facilitating the reaction.

In a compound of formula (V) the halogen W is preferably iodine. The alkylation reaction of a compound of formula (IV) with a compound of formula (V) can be carried out in a suitable organic solvent, such as a C_1-C_4 alcohol, e.g. methanol, ethanol or isopropanol, in particular in ethanol, at a temperature ranging from about 0°C to about 50°C.

The alkylation reaction of a compound of formula (IV) with an aldehyde of formula (VI) can be carried out in a suitable solvent, such as a C_1-C_4 alcohol, e.g. methanol, ethanol or acetonitrile in the presence of a suitable reducing agent, such as sodium cyanoborohydride, at a temperature ranging from about 0°C to about 30°C.

A compound of the invention can be converted, as stated above, into another compound of the invention by known methods. Process-variant b) above may be regarded as an example of optional conversion of a compound of the invention into another compound of the invention.

An isomer, e.g., a d- or l-isomer of a compound of the invention can be separately synthesized from optically pure starting material or separated from a racemate in a conventional manner.

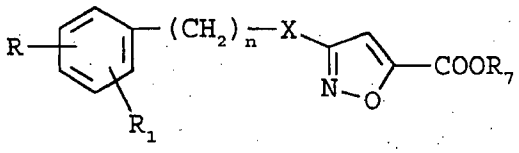
Also the optional salification of a compound of the invention as well as the conversion of a salt into the free compound may be carried out by conventional methods.

When in the compounds of the present invention and in the intermediate-products thereof, groups are present, which need to be protected before submitting them to the hereabove illustrated reactions, they may be protected before being reacted and then deprotected according to methods well known in organic chemistry.

The compounds of formula (III), (V) and (VI) are known

compounds or can be obtained by known methods.

A compound of formula (II) can be obtained from reduction of a compound of formula (VII)

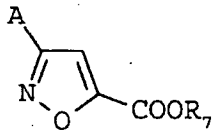


(VII)

where R, R_1, X and n are as defined above and R_7 is a lower alkyl, typically C_1-C_4 alkyl.

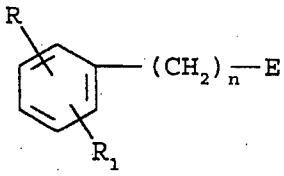
Transformation to aldehyde can be achieved using a suitable reducing agent such as i-Bu_2AlH, $LiAlH_4$, $NaAlH_4$, preferably i-Bu_2AlH in toluene at about -75°C.

A compound of formula (VII) can be obtained reacting a compound of formula (VIII)



(VIII)

where A is OH, halogen or a leaving group such as mesyloxy, tosyloxy or trifluoroacetate and R_7 is as defined above, with a compound of formula (IX)



(IX)

where E is NH_2, S^-M^+ wherein M is an alkali metal, or E is halogen or a leaving group such as mesyloxy, tosyloxy or trifluoroacetate and R, R_1 and n are as defined above.

In particular if a compound of formula (VII) is desired in which X is -O-, then in the starting compound of formula (VIII) A is OH and in the compound of formula (IX) E is halogen or a leaving group such as mesyloxy, tosyloxy or trifluoroacetate. The reaction between such a compound of formula (VIII) (commercially available when R_7 = Me) and a

compound of formula (IX) can be performed using a suitable base such as anhydrous potassium carbonate, sodium carbonate, triethylamine, pyridine, diisopropylethylamine, etc., in a suitable solvent such as ethanol, acetonitrile, methanol, dimethylformamide, toluene, acetone, at a suitable temperature from about 0°C to about 110°C, preferably about 60°C, for about 3 hours to about 8 hours.

When a compound of formula (VII) is desired in which X is NH, then in the compound of formula (VIII) A is halogen or a leaving group such as mesyloxy, tosyloxy or trifluoroacetate, and in the compound of formula (IX) E is NH_2. Alkylation of such a compound of formula (IX) is accomplished under suitable conditions, e.g. in a solvent such as benzene, pyridine, acetonitrile, etc., at a temperature between about 20°C to about 120°C, in the presence or in the absence of a suitable base, e.g. 1,8-diazabicyclo[5.4.0]undec-7-ene, triethylamine, etc.

When a compound of formula (VII) is desired in which X is -S-, then in the compound of formula (VIII) A is halogen or a leaving group such as mesyloxy, tosyloxy or trifluoroacetate, and in the compound of formula (IX) E is S^-M^+ in which M is an alkali metal, e.g. sodium or potassium. An alkali metal salt of formula (IX) can be reacted with such a compound of formula (VIII) in polar organic solvents such as dimethylsulfoxide, dimethylformamide, acetonitrile, etc., at a temperature between about 20°C to about 160°C for about 1 hour to about 30 hours.

Compounds of formula (VIII) and (IX) are known compounds or can be obtained following methods known in the literature (e.g. Houben-Weyl; Band E 8 a; 45-225).

Pharmacology

The compounds of the invention are active on the central nervous system (CNS) and can be used in therapy, for example as antiepileptics, in the treatment of Parkinson's disease and as neuroprotective agents, e.g. preventing or treating neuronal loss associated with stroke, hypoxia, ischemia, CNS trauma, hypoglycaemia or surgery and in treating and preventing neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, Down's syndrome, Huntington's disease, dementia caused by acquired immunodeficiency syndrome (AIDS), infarctual dementia; they can also be used as antidepressants, hypnotics and antispastic agents and in treating ocular damage, rethinopaty and infections or inflammations in the brain. The activity on the CNS of the compounds of the invention was evaluated on the basis of pharmacological methods, such as, for example, the antagonism of convulsions and lethality induced by intravenous injection of bicuculline in mice (Antiepileptic Drugs, D.M. Woodbury et al. eds., 2nd edition, Raven Press, New York, 1982), or the antagonism of maximal electroshock seizures (MES) (Woodbury, L.A. and Davenport, V.D., Arch. Int. Pharmacodyn. Ther. 92; 97-104, 1952).

A patient is treated according to the present invention by a method comprising administering to the patient an effective amount of one of the compounds of the invention. In this way the present compounds can be used to treat disorders of the central nervous system, for example epilepsy or Parkinson's disease; or as neuroprotective agents, and in preventing neurodegenerative diseases or treating a patient suffering therefrom, as anti-depressants, hypnotics, anti-spastic agents and for the

treatment of ocular damage or rethinopaty and infections or inflammations in the brain. The condition of a patient may thus be improved.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous injection or infusion.

The dosage depends on the age, weight, conditions of the patient and on the administration route; for example, the dosage adopted for oral administration to adult humans e.g. for the representative compound of the invention 2-[3-(3-fluorobenzyloxy)-isoxazol-5-ylmethylamino]-propanamide may range from about 1 to about 500 mg pro dose, from 1 to 5 times daily.

The invention includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as an active principle, in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl

pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspension.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerin and/or mannitol and/or sorbitol.

The suspension and the emulsion may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscolar injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the

invention.

Example 1

Methyl 3-(3-fluorobenzyloxy)-5-isoxazolecarboxylate (1)

Methyl 3-hydroxy-5-isoxazolecarboxylate(5.0 g; 0.035 mol) was dissolved in acetone (90 ml) under nitrogen, K_2CO_3 (9.4 g; 0.068 mol) was added and the mixture was heated to reflux for one hour. After addition of KI (a catalitic amount), 3-fluorobenzylchloride (6.3 ml, 0.053 mol) was added dropwise and the mixture was stirred at reflux for 5 hours. The reaction mixture was filtered, the solution was evaporated to give a residue which was directly flash chromatographed on silica gel (eluant: hexane 3 : ethyl acetate 1) to afford a white solid (6.5 g; 74%; m.p. 55-56°C).

^{1}H-NMR (δ, $CDCl_3$): 3.95 (s, 3H, $COOCH_3$), 5.3 (s, 2H, CH_2O), 6.58 (s, 1H, CH isox.), 7.0-7.41 (m, 4H, arom.)

Analogously the following compounds can be prepared:

Methyl 3-(3-bromobenzyloxy)-5-isoxazolecarboxylate;

Methyl 3-(3-chlorobenzyloxy)-5-isoxazolecarboxylate;

Methyl 3-(4-fluorobenzyloxy)-5-isoxazolecarboxylate; and

Methyl 3-(2-fluorobenzyloxy)-5-isoxazolecarboxylate.

Example 2

3-(3-Fluorobenzyloxy)-5-isoxazolecarboxaldehyde (2)

Compound (1) (4.0 g, 0.016 mol) was dissolved in dry toluene (80 ml) under nitrogen. The solution was cooled to -75°C and 16 ml (0.019 mol) of 1.2 M DIBAH in toluene were added dropwise. The solution was stirred for 1 h and then quenched with 20 ml of 2 N HCl. The mixture was allowed to warm to room temperature and diluted with ethyl acetate. The organic layer was removed and washed with brine and

then dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (eluant: hexane 9 : ethyl acetate 1) to afford an oil (2.5 g; 71%).

^{1}H-NMR (δ, DMSO): 5.32 (s, 2H, CH_2O), 7.2 (s, 1H, CH isox.), 7.15-7.5 (m, 4H, arom.), 9.78 (s, 1H, CHO).

Analogously, the following products can be obtained starting from the corresponding ester:

3-(3-Chlorobenzyloxy)-5-isoxazolecarboxaldehyde;

3-(3-Bromobenzyloxy)-5-isoxazolecarboxaldehyde;

3-(4-Fluorobenzyloxy)-5-isoxazolecarboxaldehyde;

3-(2-Fluorobenzyloxy)-5-isoxazolecarboxaldehyde;

3-(3-Fluorobenzylamino)-5-isoxazolecarboxaldehyde; and

3-Benzylsulfanyl-5-isoxazolecarboxaldehyde.

Example 3

(S)-2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide, methanesulfonate (3)

To a solution of (S)-2-aminopropanamide hydrochloride (1.0 g; 0.008 mol) in anhydrous methanol (40 ml), under stirring and nitrogen, 1.0 g of 3Å molecular sieves were added and then, in a single portion, $NaBH_3CN$ (0.4 g; 0.006 mol); after 20 minutes, 1.7 g (0.008 mol) of compound (2) were added, in 20 ml of anhydrous methanol. After three hours the reaction was completed, the mixture filtered, the solution was evaporated to give a residue which was directly flash-chromatographed on silica gel (eluant: $CHCl_3$ 100 : CH_3OH 2 : 30% NH_4OH 0.15) to afford a white solid (0.78 g; 35%). The free base thus obtained was treated with a stoichiometric amount of methanesulfonic acid to yield the title compound (m.p. 160-165°C; $[\alpha]_D^{25}$ +10.9 (c=1.3, AcOH)).

^{1}H-NMR (δ, DMSO): 1.4 (d, 3H, CH-$\underline{CH_3}$), 2.3 (s, 3H, $CH_3SO_3^-$),

3.85 (q, 1H, $\underline{CH}$-CH_3), 4.3 (s, 2H, $\underline{CH_2}$-NH_2^+), 5.3 (s, 2H, CH_2-O), 6.5 (s, 1H, CH isox.), 7.1-7.5 (m, 4H, arom.), 7.65 and 7.95 (2xs, 2H, $CONH_2$), 9.5 (bs, 2H, NH_2^+).

Analogously, the following products can be obtained, starting from the corresponding aldehyde and the appropriate amide:

(S)-2-[3-(3-chlorobenzyloxy)isoxazol-5-ylmethylamino] propanamide, methanesulfonate;

(S)-2-[3-(3-bromobenzyloxy)isoxazol-5-ylmethylamino] propanamide, methanesulfonate;

(S)-2-[3-(4-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide, methanesulfonate;

(S)-2-[3-(2-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide, methanesulfonate;

(S)-2-[3-(3-fluorobenzylamino)isoxazol-5-ylmethylamino] propanamide, methanesulfonate;

(S)-2-[3-(benzylsulfanyl)isoxazol-5-ylmethylamino] propanamide, methanesulfonate;

(S)-2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino]-N-methyl-propanamide, methanesulfonate; and

2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino]-2-methyl-propanamide.

Example 4

(S)-2-{[3-(3-fluorobenzyloxy)isoxazol-5-ylmethyl] methylamino}propanamide

0.50 g (0.0017 mol) of compound (3) (free base) are dissolved in acetonitrile (30 ml) under a nitrogen stream. To this mixture, 0.7 ml (0.0086 mol) of 37% formaldehyde and 0.16 g (0.0025 mol) of sodium cyanoborohydride are

added at room temperature. After 20 minutes, glacial acetic acid is dropped up to neutrality of the solution. The mixture is stirred for 40 minutes and evaporated to dryness. 20 ml of 2N KOH are added to the residue. After extracting with ethyl acetate, washing with N/2 KOH and then with water and brine, the organic layer is dried on Na_2SO_4, then filtered and evaporated to obtain a residue which is flash-chromatographed on silica gel (eluant: $CHCl_3$ 200 : CH_3OH 3 : 30% NH_4OH 0.2) to give 0.35 (67%) of a white solid.

Analogously, the following products can be prepared starting from the corresponding secondary amine:

(S)-2-{[3-(3-chlorobenzyloxy)isoxazol-5-ylmethyl] methylamino}propanamide; and

(S)-2-{[3-(3-bromobenzyloxy)isoxazol-5-ylmethyl]methylamino} propanamide.

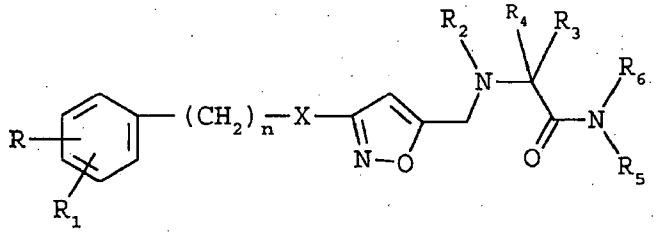
Example 5

With the usual methods of pharmaceutical technique, preparation can be made of capsules having the following composition:

(S)-2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino]propanamide, methanesulfonate	50 mg
Talc powder	2 mg
Corn starch	2 mg
Microcristalline cellulose	6 mg
Magnesium stearate	1 mg

CLAIMS

1. An isoxazole derivative having the following formula (I)



(I)

wherein:

n is zero or an integer of 1 to 3;

X is O, S or NH;

each of R and R_1, which are the same or different, is hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_4 alkoxy or trifluoromethyl;

each of R_2, R_5 and R_6 , which are the same or different, is hydrogen or C_1-C_6 alkyl;

each of R_3 and R_4, which are the same or different, is hydrogen or C_1-C_6 alkyl, or R_3 and R_4 taken together with the adjacent carbon atom form a C_3-C_7 cycloalkyl ring;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

n is 1 or 2;

R is hydrogen;

R_1 is hydrogen or halogen; and

each of R_2, R_3, R_4, R_5 and R_6, which are the same or different, is hydrogen or C_1-C_4 alkyl.

3. A compound according to claim 1, wherein

n is 1;

X is O or NH;

R_1 is hydrogen or halogen;

R_3 is C_1-C_4 alkyl;

R_4 is hydrogen or C_1-C_4 alkyl; and

R, R_2, R_5 and R_6 are hydrogen.

4. A compound selected from:

2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide;

2-[3-(3-chlorobenzyloxy)isoxazol-5-ylmethylamino] propanamide;

2-[3-(3-bromobenzyloxy)isoxazol-5-ylmethylamino]propanamide;

2-[3-(4-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide;

2-[3-(2-fluorobenzyloxy)isoxazol-5-ylmethylamino] propanamide;

2-[3-(3-fluorobenzylamino)isoxazol-5-ylmethylamino] propanamide;

2-[3-(benzylsulfanyl)isoxazol-5-ylmethylamino]propanamide;

2-{[3-(3-fluorobenzyloxy)isoxazol-5-ylmethyl]methylamino} propanamide;

2-{[3-(3-chlorobenzyloxy)isoxazol-5-ylmethyl]methylamino} propanamide;

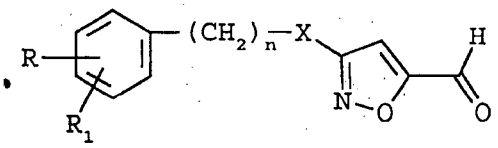
2-{[3-(3-bromobenzyloxy)isoxazol-5-ylmethyl]methylamino} propanamide;

2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino]-N-methyl-propanamide;

2-[3-(3-fluorobenzyloxy)isoxazol-5-ylmethylamino]-2-methyl-propanamide; and the pharmaceutically acceptable salts thereof; and wherein the compounds may, when appropriate, exist either as a single S- or R-isomer or isomers thereof.

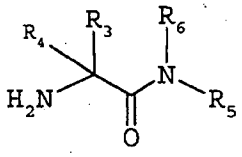
5. A process for producing a compound as defined in claim 1, which process comprises:

a) reacting a compound of formula (II)



(II)

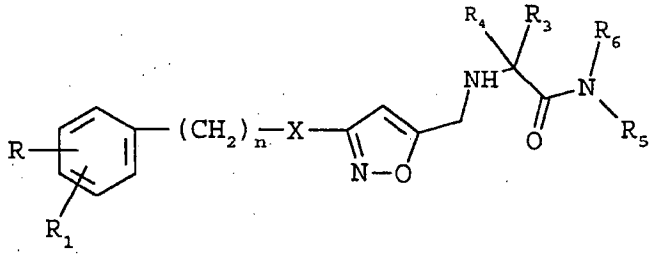
wherein n, R, R_1 and X are as defined in claim 1, with a compound of formula (III)



(III)

wherein R_3, R_4, R_5 and R_6 are as defined in claim 1, thus obtaining a compound of formula (I) in which R_2 is hydrogen; or

b) reacting a compound of formula (IV)



(IV)

wherein R, R_1, R_3, R_4, R_5, R_6, n and X are as defined in claim 1, with a compound of formula (V) or (VI)

R'_2W (V) R''_2CHO (VI)

wherein W is a halogen atom, R'_2 is a C_1-C_6 alkyl and R''_2 is hydrogen or C_1-C_5 alkyl, thus obtaining a compound of the invention in which R_2 is C_1-C_6 alkyl; and, if desired, converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of

isomers of a compound of the invention into the single isomer.

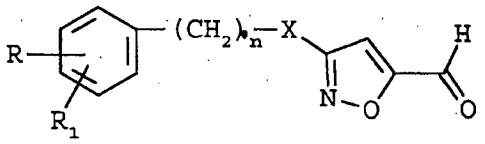
6. A pharmaceutical composition comprising a compound as defined in claim 1 as an active principle, and a pharmaceutically acceptable excipient.

7. A compound as defined in claim 1 for use as an active therapeutic substance.

8. A compound as claimed in claim 7 for use as an antiepileptic agent, in the treatment of Parkinson's disease, as a neuroprotective agent or in treating or preventing neurodegenerative diseases.

9. A compound as claimed in claim 7 for use as an antidepressant, a hypnotic or antispastic agent, or in treating ocular damage or retinopathy.

10. A compound of formula (II)



(II)

wherein R, R_1, n and X are as defined in claim 1.

11. A method of treating a patient in need or a neuroprotective, anti-depressant, hypnotic or anti-spastic agent or suffering from epilepsy, Parkinson's disease, neurodegenerative diseases, ocular damage, rethinopaty or infectious or inflammations in the brain, the method

comprising administering to said patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/01928

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D261/12 C07D261/14 C07D261/10 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 22808 A (FARMITALIA CARLO ERBA S.R.L.) 13 October 1994 see claims	1-11
A	EP 0 371 876 A (NOVAPHARME) 6 June 1990 see claims	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 1998	22.07.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/01928

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/EP 98/01928

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